53. **[TWICE-AMENDED]** The kit of Claim 51, comprising a recombinant immunoglobulin heavy chain binding protein having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2.

REMARKS

Claims 22, 30, 33, 34, 40-44, 46-53 have been amended herein. Claims 18, 22-24, 30, 32-34, and 40-54 remain in the case. Entry of this Response After Final and favorable reconsideration is respectfully requested.

The following remarks address the issues presented in the Office Action in the order of their appearance.

Suggested Arrangement of the Specification:

Applicants have inserted into the specification the conventional headings suggested by the Examiner. Applicants have also recast the legends to the figures, presented at page 30 of the application as filed, as an integrated section under the heading "BRIEF DESCRIPTION OF THE DRAWINGS."

Applicants have also reviewed the specification and corrected a number of minor typographical errors.

Objections to Claims:

The objections noted in paragraphs 12-14 of the Office Action dated 12/16/2002 (Paper 17) have been addressed by appropriate amendment to the claims. Specifically, the typographical errors in Claims 47, 49, and 52 have been rectified. Claims 33 and 42 have been recast as independent claims that contain all of the limitations of the base claims and any intervening claims.

Rejection of Claims 22-24 and 44-53 Under 35 USC §112, First Paragraph:

This rejection is believed to have been overcome by appropriate amendment to the claims. Specifically, in each of Claims 22-24 and 44-53, the phrase "fragment thereof" has been removed from the claim.

In light of the amended claim language, Applicants respectfully submit that this rejection is no longer tenable. Withdrawal of the same is requested.

Rejection of Claims 22 and 23 Under §102(b) Over Kozutsumi et al.:

This rejection is respectfully traversed because, as noted earlier, Kozutsumi et al. fail entirely to describe a pharmaceutical composition for the treatment of any disease state, as is recited in the present claims. Applicants acknowledge that the Office is correct in that the fusion protein described by Kozutsumi includes the full length of the GRP78 protein. However, and as noted earlier, Kozutsumi's composition is an inoculant that contains ingredients that are anathema to a "pharmaceutically-acceptable carrier." In short, Kozutsumi et al. fail entirely to disclose a "pharmaceutically-acceptable carrier" for the fusion protein described therein.

Specifically, a pharmaceutically-acceptable carrier for an active pharmaceutical ingredient destined for humans **would never** include Freund's adjuvant, especially the complete version of Freund's adjuvant. As noted earlier, Kozutsumi fabricated an **inoculant** to raise antibodies, not a pharmaceutical composition. As such, Kozutsumi's composition includes a carrier that is not pharmaceutically acceptable because it contains Freund's Complete Adjuvant. A "pharmaceutically-suitable carrier" is a positive limitation of Claim 22. Thus, Applicants submit that this rejection is improper because Kozutsumi et al. fail to disclose a composition containing BiP(GRP78) and a pharmaceutically-suitable carrier.

Specifically addressing the Freund's complete adjuvant, note that Kozutsumi explicitly teaches the use of Freund's complete adjuvant for the first injection and Freund's incomplete adjuvant for the subsequent injections. See page 118 of Kozutsumi, bottom paragraph. The Kozutsumi et al. document explicitly requires the use of Freund's Complete Adjuvant.

Freund's Complete Adjuvant, however, is unacceptable in a "pharmaceutically-suitable" carrier. In this regard, see Exhibit A, attached hereto and incorporated herein by reference. Exhibit A is a copy of the current Policies and Procedures for the Use of Complete Freund's Adjuvant, as promulagated by Emory University, Atlanta, Georgia. In particular, note page 3, under the heading "Potential Hazards to Research Personnel":

> Special care must be taken to avoid parenteral exposure of personnel involved in the preparation and administration of CFA. Accidental intradermal or intramuscular inoculation of the mycobacterial-in-oil suspensions may result in tuberculin sensitization of tuberculin-negative individuals and moderate to severe local, regional, or systemic hypersensitivity reactions in individuals who are sensitized to tuberculin. Persons who have had tuberculosis may develop chronic ulcerating granulomas following injection of very small amounts of CFA. Inadvertent ocular exposure can lead to blindness.

As is clear from this passage, Complete Freund's Adjuvant is not considered part of a "pharmaceutically-suitable carrier" as required by the present claims.

Because the Kozutsumi et al. reference fails to describe a composition that includes a pharmaceutically-acceptable carrier, Applicants respectfully submit that the rejection of Claims 22 and 23 under §102(b) over Kozutsumi et al. is improper. Withdrawal of the same is respectfully requested.

Rejection of Claims 44, 48, and 51 Under 35 USC §102(b) in View of U.S. Patent No. 5,188,964 (McGuire et al., "the '964 Patent") and Rejection of Claim 45 Under 35 USC §103 in View of the '964 Patent:

Applicant's undersigned counsel acknowledges the discrepancy between the argument presented in his last response and the actual language of the claims. Counsel requests that the Office disregard the prior remarks presented with regard to these two rejections and submit in its place the following traversal.

Due to the similarity of these two rejections, they will be addressed simultaneously.

This rejection is respectfully traversed because the "protein standards" disclosed by the '964 Patent do not include a BiP(GRP78) protein, nor does this reference teach, suggest, or motivate using a BiP(GRP78) protein in the test kits actually disclosed therein.

The Office's attention is directed specifically to the '964 Patent, column 17, lines 7-20:

> Kits useful in the present invention comprise a carrier having compartments to receive several closed containers, the number depending on the specific reagents required for the method of analysis. **All kits would provide a first container means comprising a stress response protein standard which contains known levels of hsp27, 70, 90 and grp 94**; a second container means comprising a negative control breast tumor extract, a third container means comprising a positive control breast tumor extract, and a fourth container means comprising four monoclonal antibodies to the four stress response proteins Methods of stress response protein determination could be based on Western Blot, ELISA, or immunohistochemical analysis. (Emphasis added.)

Conspicuously absent from this list is GRP78, despite the fact that GRP78 was known to the inventors of the '964 Patent. Moreover, throughout the Summary of the Invention and the Detailed Description, the '964 Patent lists the significance of "hsp 27, 70, 90 and/or grp 94" and fails to mention, in even a single instance, GRP78. In fact, this list of four specific proteins (hsp 27, 70, 90 and/or grp 94) is listed multiple times throughout the '964 Patent:

column 7, line 66

column 8, line 1

column 8, line 10

column 8, lines 44-45

column 8, line 50 (referencing "the four srp's")

column 9, line 24

column 10, line 16

column 11, line 55-60

column 12, line 10-15

column 12, lines 59-65 (fails to note any correlation involving GRP78)

column 15, lines 25-33

column 16, lines 60-65 "The four srp's analyzed...."

column 17, lines 7-20 (quoted above)

column 17, lines 10-15.

In short, the '964 Patent discloses a predictive relationship for breast cancer that involves only hsp 27, 70, 90 and/or grp 94. This document is wholly silent regarding any predictive power or use for GRP78 in the invention disclosed therein. In short, the kit disclosed by the '964 Patent does not include a GRP78 protein. Therefore, the rejection of Claim 44 under §102(a) in view of the '964 Patent is improper on its face.

Applicants further submit that the Office has not presented a *prima facie* case of obviousness with respect to any of Claims 44, 45, 48, and 51 because the '964 Patent does not suggest or motivate inserting a GRP78 Protein into the kit that is actually disclosed in this patent.

As noted above, the '964 Patent acknowledges the existence of GRP78, but fails to ascribe any significance to it. Specifically, note that the discussion with regard to GRP78 in the '964 Patent is presented wholly within the discussion of the prior art. Applicants acknowledged that the '974 Patent notes a "relationship" between HSP's and GRP's (see column 2, lines 19-27), but the document does not elaborate on the nature of that relationship in any fashion.

Moreover the document explicitly acknowledges that GRP78 is different from the other HSP's actually recited as "protein standards" in the passage from column 17 quoted previously. See, for example, column 5, line 52, where it is noted that "Grp 78 is about 60% homologous to hsp 70." Note also that the Office has already acknowledged that hsp70 is a distinct protein from BiP(GRP78). The document certainly does not teach or suggest that BiP(GRP78) would function in the kit actually disclosed therein. If it would work, why then isn't GRP78 listed among the protein standards in the '964 Patent?

It is not listed, Applicants submit, because the inventors of the '964 Patent did not establish a predictive link between GRP78 and breast cancer, and therefore the GRP78 protein is not operational in the method disclosed in the '964 Patent.

If this is the case, Applicants further traverse the rejection under §103 because there is no technical motivation to make a suggested change, if the change suggested by the Office

would destroy the utility of the invention disclosed in the prior art. In this case, the Office is asserting that it would have been obvious to use GRP78 in the kit actually disclosed by the '964 Patent. But the inventors of the '964 Patent themselves do not make this connection, even though they were aware of the GRP78 protein. In short, there is nothing within the '964 Patent to suggest that GRP would work in the test disclosed therein. Moreover, based upon the multiple listing of the four proteins that do function, it seems that the inventors of the '964 Patent chose their words carefully to exclude GRP78 from the scope of "protein standards" as that phrase is disclosed in the '964 Patent.

For these reasons, Applicants submit that the rejection of Claims 44, 45, 48, and 51 under §103(a) in view of the '964 Patent is improper. Withdrawal of the same is respectfully requested.

Rejection of Claims 44-46, 49, and 52 Under 35 USC §103 in View of the '964 Patent in Combination With Hsu et al. or Sambrook et al.:

As in the previous rejection, Applicants' undersigned counsel acknowledges the discrepancy between the argument presented in his last response and the actual language of the claims. Counsel requests that the Office disregard the prior remarks presented with regard to this two rejection and submits in its place the following traversal.

Applicants traverse this rejection because, as noted above, the primary reference, the '964 Patent, does not disclose or suggest a kit containing a GRP78 protein. The arguments presented in the prior section are repeated here in their entirety. By way of summary, the '964 Patent discloses a predictive relationship for breast cancer that involves only hsp 27, 70, 90 and/or grp 94. The document does not disclose or suggest any predictive power or use for GRP78 in the invention disclosed therein. In short, the kit disclosed by the '964 Patent does not include a GRP78 protein.

Combining the '964 Patent with Hsu et al. and/or Sambrook et al. does not cure this deficiency because the **combined** references also fail to teach using a GRP78 protein in a test kit.

Applicants therefore submit that the Office has failed to establish a *prima facie* case of obviousness with regard to Claims 44-46, 49, and 52. It is therefore requested that the rejection of these claims under 35 USC §103 in view of the '964 Patent in combination with Hsu et al. or Sambrook et al. be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

3/14/2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. Serial No.: 09/806,955 Group Art Unit: 1644

Filed: 07/11/2001 Examiner: Jamroz, M.

Applicants: Panayi et al. Attorney Docket No.: 78104.023

Title: **TREATMENT OF INFLAMMATORY DISEASE**

"MARKED UP" CLAIMS AS AMENDED, 37 CFR §1.121(c)(1)(ii)

18. [AMENDED] A recombinant immunoglobulin heavy chain binding protein designated BiP(GRP78) and having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2.

22. **[TWICE-AMENDED]** A pharmaceutical composition for the treatment of rheumatoid arthritis in mammals, including humans, the composition comprising an anti-rheumatoid-arthritic amount of an isolated immunoglobulin heavy chain binding protein designated BiP(GRP78) **[or a fragment thereof]**, in combination with a pharmaceutically-suitable carrier.

23. [AMENDED] The pharmaceutical composition of Claim 22, wherein the immunoglobulin heavy chain binding protein is a recombinant immunoglobulin heavy chain binding protein.

24. The pharmaceutical composition of Claim 22, wherein the immunoglobulin heavy chain binding protein has an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2.

30. **[TWICE-AMENDED]** A method for treating rheumatoid arthritis in a mammalian subject in need thereof, including a human subject, the method comprising

administering to the subject an anti-rheumatoid-arthritic amount of immunoglobulin heavy chain binding protein designated BiP(GRP78) **[or a fragm nt thereof]**.

32. [AMENDED] The method of Claim 30, wherein a recombinant immunoglobulin heavy chain binding protein is administered to the subject.

33. **[TWICE-AMENDED]** [Allowed] **[The method of Claim 32, wherein]** **A method for treating rheumatoid arthritis in a mammalian subject in need thereof, including a human subject, the method comprising administering to the subject an anti-rheumatoid-arthritic amount of** a recombinant immunoglobulin heavy chain binding protein having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID NO: 2 **[is administered to the subject]**.

34. **[AMENDED]** The method of Claim **[30]** **33**, wherein the immunoglobulin heavy chain binding protein is administered orally, nasally, subcutaneously, or intravenously.

40. **[TWICE-AMENDED]** A method for diagnosing the presence of rheumatoid arthritis in a mammalian subject, including a human subject, the method comprising contacting a bodily fluid from the subject selected from the group consisting of whole blood, blood plasma, blood serum, saliva, mucus, synovial fluid, and cerebrospinal fluid, **[to]** **with** immunoglobulin heavy chain binding protein designated BiP(GRP78) **[or a fragment thereof]**, and then ascertaining the presence or absence of anti-immunoglobulin heavy chain binding protein antibodies in the bodily fluid tested, the presence of antibodies indicating the presence of rheumatoid arthritis in the subject.

41. **[TWICE-AMENDED]** The method of Claim 40, wherein the bodily fluid is contacted with **[a]** **a** recombinant immunoglobulin heavy chain binding protein

42. **[TWICE-AMENDED]** [Allowed] [The method of Claim 40, wherein] **A method f r diagn sing the presence of rheumatoid arthritis in a mammalian subject, including a human subject, the method comprising contacting a bodily fluid from the subject selected from the group consisting of whole blood, blood plasma, blood serum, saliva, mucus, synovial fluid, and cerebrospinal fluid, to an immunoglobulin heavy chain binding protein, wherein** the bodily fluid is contacted with an immunoglobulin heavy chain binding protein having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2.

43. **[TWICE-AMENDED]** The method of Claim **[40]** **42**, wherein the presence of **[an]** anti-immunoglobulin heavy chain binding protein antibodies is ascertained using an enzyme-linked immunosorbent assay (ELISA) incorporating an immunoglobulin heavy chain binding protein **[or a fragment thereof]**.

44. **[TWICE-AMENDED]** A kit for diagnosing the presence of rheumatoid arthritis in a mammalian subject, including a human subject, the kit comprising:

an amount of an isolated immunoglobulin heavy chain binding protein designated BiP(GRP78) **[or a fragment thereof]**, disposed in a suitable container.

45. The kit of Claim 44, further comprising instructions for use of the kit.

46. **[TWICE-AMENDED]** The kit of Claim 44, comprising a recombinant immunoglobulin heavy chain binding protein **[or a fragment thereof]**.

47. **[TWICE-AMENDED]** The kit of Claim 44, comprising **an** immunoglobulin heavy chain binding protein having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2 **[or a fragment thereof]**.

48. **[TWICE-AMENDED]** The kit of Claim 44, comprising an enzyme-linked immunosorbent assay that incorporates the immunoglobulin heavy chain binding protein **[r the fragm nt thereof]**.

49. **[TWICE-AMENDED]** The kit of Claim 48, comprising **[a]** a recombinant immunoglobulin heavy chain binding protein **[or a fragment thereof]**.

50. **[TWICE-AMENDED]** The kit of Claim 48, comprising a recombinant immunoglobulin heavy chain binding protein having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2 **[or a fragment thereof]**.

51. **[TWICE-AMENDED]** The kit of Claim 44, comprising a Western Blot assay that incorporates the immunoglobulin heavy chain binding protein **[or the fragment thereof]**.

52. **[TWICE-AMENDED]** The kit of Claim 51, comprising **[a]** a recombinant immunoglobulin heavy chain binding protein **[or a fragment thereof]**.

53. **[TWICE-AMENDED]** The kit of Claim 51, comprising a recombinant immunoglobulin heavy chain binding protein having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2 **[or a fragment thereof]**.

54. An isolated polypeptide having an amino acid sequence as shown in SEQ. ID. NO: 1 or SEQ. ID. NO: 2.